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### Field of the invention

5 The present invention relates to an oral pharmaceutical dosage form comprising a substance with inhibiting effect on the ileal bile acid transport system (IBAT). More specifically, the dosage form is suitable in the treatment of hypercholesterolaemia. The invention also relates to manufacturing processes and the use of the dosage form in the treatment of hypercholesterolaemia. A further aspect of the invention is the use of a substance with inhibiting effect on IBAT in combination with a bile acid binder by  
10 simultaneously, separately or sequentially administration of the two substances, and the use of these substances in the manufacture of such a pharmaceutical dosage form.

## Background and Prior Art.

15 It is well-known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous  
20 established therapies to reduce the concentration of cholesterol involve for instance treatment with HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy involve the treatment with substances with inhibiting effect on the ileal bile acid transport  
25 system (IBAT).

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by an active transport mechanism called ileal bile acid transport (IBAT). Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia. See for instance "Interaction of bile acids and cholesterol with

nonsystemic agents having hypocholesterolemic properties", *Biochemica et Biophysica Acta*, 1210 (1994) 255- 287. Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

5 Several chemical compounds possessing such IBAT activity have recently been described, see for instance hypolipidaemic benzothiazepine compounds described in WO 93/16055 and WO 96/16051; condensed 1,4-thiazepines described in WO 94/18183; different heterocyclic compounds described in WO 94/18184; and 1,4-benzothiazepine-1,1-dioxides described in WO 96/05188.

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Further, especially suitable compounds for the present invention are for instance benzothiazepines with IBAT activity described in WO 96/08484; bile acid resorption inhibitors described in WO 97/33882, WO 98/07449, WO 98/03818, EP 864582, EP 489423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, and EP 624 596.

15

It is proposed that these types of compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals. For instance, the dosage forms can be a daily dose which is administered once a day or being divided to be administered several times a day, or alternative in a sustained release form. Suitable  
20 dosage forms are intended for oral administration.

In general, pharmaceutical drug substances will be absorbed in the upper small intestine, and therefore only a small amount will reach ileum when administered in a conventional oral dosage form. Irrespectively of the construction of the pharmaceutical dosage form, it  
25 should provide contact for the active compound, e.g. inhibitor of IBAT, with the compound's site of action in the body, for example in the ileum. The above prior art documents discuss in general terms suitable pharmaceutical dosage forms for the described IBAT inhibitor compounds. However, none of the document describes a specific way to obtain a release of the active substance directly to or close to the site of action.

30

Contact between the active drug and the site of action can be established in different ways. The present application describes a new pharmaceutical dosage form which reduces and minimises absorption, metabolism and dilution in the luminal content of the IBAT inhibitor in the body before the active substance (IBAT inhibitor compound) reaches its site of  
5 action.

It has been proposed that after absorption over the gastro-intestinal membrane, an IBAT inhibitor could interact with transport systems similar to IBAT for instance the corresponding transport system in the liver (LBAT) or could provide other non-specific  
10 systemic effects which could lead to undesirable pharmacological or even toxicological effects. This could severely limit the clinical usefulness of IBAT inhibitors especially in the treatment of hypercholesterolaemia, i.e. conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol.

15 The inhibition of the re-absorption of bile acids from the small intestine performed by an effective IBAT inhibitor may lead to increased levels of bile acids in the lower parts (colon) of the gastro-intestinal tract. Such an increase of bile acid concentrations in the distal regions could potentially generate diarrhoea and discomfort to the patient. The present invention provides a new approach to minimise the concentration of free bile acids  
20 in the colon and thereby reduce the potential risk of adverse events by co-administration of a bile acid binder together with the IBAT inhibitor. However, the combination of an IBAT inhibitor and a bile acid binder have previously been proposed in the above patent applications describing new IBAT inhibitor compounds. The purpose of such previously described combinations have been to enhance the cholesterol lowering efficacy of the  
25 therapy, and there is no hint that such a combination could be used to minimise a potential risk for diarrhoea connected with IBAT inhibitor therapy.

#### Brief description of the invention.

The aim of the present invention is to reduce the problem with undesirable side-effects of IBAT inhibitor compounds by providing a pharmaceutical formulation which reduces the systemic drug bioavailability while maintaining or enhancing the cholesterol lowering effect of the drug. Such undesirable systemic effects put a load on other organs, e.g. liver and kidneys. Thus, the present dosage form provides a reduced, i.e. minimum absorption, metabolism and dilution in the luminal content of the IBAT inhibitor by a specific targeting to the site of action. The release is directed specifically to the site of action which reduces or even might avoid toxicological effects of the drug. The formulation is intended to be orally administered and pass through the upper part of the small intestine with a minimum of release of the IBAT inhibitor before it reaches the distal jejunum or proximal ileum.

The present invention provides such a dosage form which delivers the main part of the dose to the site of action, i.e. in the distal jejunum, in the proximal ileum or in the distal ileum. The release of the drug is thereby reduced or minimised to more proximal parts, the duodenum and jejunum, where drug absorption in general is most efficient. Thus, the release of the drug should preferably start in the distal jejunum or proximal ileum, or the entire dose should be delivered directly to the ileum.

Preferably, the formulation is an orally administered formulation, such as a delayed release formulation, which starts to release the main part of the drug in the distal jejunum or in the proximal ileum. The oral formulation might also provide protection of the drug from the acid environment in the stomach by an enteric coating. Such an enteric coating also protects the gastric mucosa from drug exposure and thereby minimises irritation or even damages of the gastric mucosa potentially caused by aggressive drug exposure.

An additional aim of the present invention is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a

secretory diarrhoea - by irritation and inflammation - as a undesired side effect caused by the treatment with an IBAT inhibitor.

Another aspect of the provided combination therapy is that the bile acid binder, for instance a resin such as cholestyramine or cholestipol, could preferably be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations is high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastro-intestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided.

15

Detailed description of the invention.

According to one aspect of the invention, an orally administered pharmaceutical formulation of an IBAT inhibitor compound is provided, which formulation releases almost the entire dose of the IBAT inhibitor compound in the distal jejunum, in the proximal ileum, or deliver the dose directly to the ileum. Such a formulation will minimise drug release in the upper part of the small intestine, i.e. above distal jejunum.

Optimal drug release and drug binding in the ileum can for instance be obtained by a delayed release formulation, such as a formulation with a specified lagtime. More specifically, less than 30 % of the drug could be released during the time the formulation spends in the stomach and in the proximal small intestine, i.e. during the passage of the upper part of the small intestine.

Thus, according to a second aspect, the present invention provides a pharmaceutical formulation with a delayed release of the IBAT inhibitor compound by a controlled lagtime. The main part of the formulation shall pass the duodenum and jejunum with a minimum release of the active dose, and thereby increasing the dose available for binding to the site of action in the ileum and thereby increasing the inhibition of the ileal bile acid transport system. Preferably, the lagtime period is about 0.5 - 2 hours calculated from emptying from the stomach, and more than 70% of the dose should be released approximately during the next 0.5 - 2.0 hours, i.e. after the lagtime period. More preferably, the dose should be released during the first hour after the lagtime period.

Dosage forms with a controlled lagtime can be constructed in different ways for instance as described in the following.

A controlled lagtime can be triggered by pH changes, redox potential differences or luminal metabolic changes in the gastro-intestinal tract as described in Aliment Pharmacol Ther 1997, 11 (suppl 3): 109-115. Such a controlled lagtime could be obtained for instance by a programmed disintegration of the formulation due to erosion, dissolution or in general by components present in the formulation interacting with the environment in the gastro-intestinal tract. Preferably, the drug release from the dosage form could be triggered by the pH variation between jejunum and ileum.

Alternatively, the drug release from the dosage form can be chronographic controlled to obtain the above specified time limits, such as for instance described in the European Patent 384642.

When the formulation reaches the distal jejunum or the ileum, the drug release should preferably be either immediately, with a sustained release or be based on a combination of such release principles. The duration of the drug release for a sustained release formulation should preferably not exceed 2 hours.

According to a third aspect of the invention, a sustained release formulation can be constructed by any known principle, such as eroding or non-eroding matrices, membrane coating layers or by diffusion or osmotically driven drug release. Suitable techniques for the construction of such formulations are for instance described in M. E. Aulton, 5 Pharmaceutics, The science of dosage form design. (1988).

An additional aspect of the invention is to combine an IBAT inhibitor compound with a bile acid binder thereby avoid a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such a diarrhoea in patients during therapy comprising IBAT inhibitor compounds.

Suitable bile acid binders for such a combination therapy are resins, such as for instance cholestyramine and cholestipol. One advantageous is that the dose of bile acid binder might be kept lower than the therapeutically dose for treatment of cholesterolemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binders any possible side effects caused by poorly tolerance of patient to the therapeutic doses also could be avoided.

A further aspect in connection with such a combination therapy, is that the bile acid binder could be administered in a dosage form with colon release, i.e. delivery of the active dose of bile acid binder in the colon. A possible risk of receiving an excess of bile acid in the colon by treatment with an IBAT inhibitor could be avoided by co-administration of a bile acid binder with colon release. Thus, any excess of bile acid in the colon, with a possible risk to cause diarrhoea, will be bound into a resin. The dose of the bile acid binder could be kept low due to an effective use of the dose by such a colon release. The colon delivery of the bile acid binder can be obtained by a formulation comprising core containing the bile acid binder and optionally pharmaceutically acceptable excipients, and coating of said core with a delayed release membrane adapted for colonic delivery. Technologies to obtain such



a delivery of drugs to the colon are for example described in Drug Development and Industrial Pharmacy 1997, 23: 893-913.

Further general aspects of the invention are that the formulations can be solid, semi-solid or liquid formulations. In a solid formulation, the carrier can be monolithic, such as tablets or capsules. One preferred monolithic formulation is a coated tablet, a capsule comprising small coated units or a multiple unit tablet comprising a multitude of small coated units. Semi-solid or liquid formulations can be administered in capsules suitable for such vehicles. The most preferred formulation is an oral formulation such as a tablet or a capsule comprising coated small units or pellets. The formulation or dosage form may contain from 0.05% to 95% of the active compound in admixture with a pharmaceutically acceptable carrier, or pharmaceutically acceptable excipients.

#### *Preparation of core material .*

The core material for the units, i.e. the tablets or the individual pellets can be constituted according to different principles. The core material may be homogenous or heterogeneous. The core containing the active principle may be differently formulated such as monolithic tablets, capsules, granules, pellets, other particles or crystals.

With a homogenous core material is meant, that it has a homogenous distribution of active substance throughout the core material.

The active substance, i.e. the IBAT inhibitor compound, is optionally mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the granulated material.

In direct compression, the ingredients are mixed and compressed by using ordinary tableting equipment.

5

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

10

For the wet granulating methods either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred, if it is possible due to the composition of the mixture.

15 Homogenous core particles can also be prepared by techniques such as dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, controlled crystallisation, supercritical crystallisation, emulsion solvent evaporation and emulsion solvent extraction.

The core material may also be produced by extrusion/ spheronization, balling or  
20 compression utilizing different process equipments.

The size of the formulated core materials is approximately between 2 and 14 mm, preferably between 3 and 9 mm for a tablet preparation, and between 0.001 and 4 mm, preferably between 0.001 and 2 mm for a pellet preparation.

25

The manufactured core material may be further layered with additional ingredients comprising the active substance and/or be used for further processing.

Alternatively, the core material may be heterogeneous with an inner zone, for instance a  
30 seed or sphere, not containing the active substance. This seed or sphere is surrounded by a

layer comprising the active substance, and optionally pharmaceutically acceptable excipients.

The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone)  
5 may be coated with an inert layer to prepare a smooth surface before the layer containing active substance is applied onto the seed/sphere.

Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water soluble seeds/spheres may comprise different  
10 inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

15 *Processes for application of delayed release membrane.*

Delayed release membrane can be applied to the core material, being a monolithic tablet, multiple units or a hard or soft gelatine capsule, by coating or layering procedures in suitable equipment such as coating pans, coating granulators or in a fluidized bed apparatus  
20 using water and/or organic solvents for the coating process. Also powder coating principles may be applied. Another possibility is to apply the coating by microencapsulation techniques such as coacervation, emulsification with subsequent removal of the solvent by extraction or evaporation, ionotropic gelation or congealing.

Such delayed release membranes may be applied on core material comprising the IBAT  
25 inhibitor for delivery to the distal small intestine and optionally also be applied to the bile acid binder for delivery to the colon.

*Pharmaceutical additives.*

Delayed release coatings may be obtained by one or more, separately or in compatible combinations of pharmaceutically acceptable ingredients, in amounts carefully titrated to reach the intended release properties. As coating layer, the following pH sensitive polymers can be applied; e.g. methacrylic acid copolymers, cellulose acetate phthalate,

5 hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s). The coating layer may also be composed of film-forming polymers being sensitive to other luminal components than pH, such as bacterial degradation or a component that has such a sensitivity when it is mixed  
10 with another film-forming polymer. Example of such components providing delayed release to the intended regions are; polymers comprising azo bond(s), polysaccharides such as pectin and its salts, galactomannans, amylose and chondroitin, disulphide polymers and glycosides.

15 The delayed release coating or an additional coating of the formulation may contain other film-forming polymers being non-sensitive to the luminal conditions for technical reasons or chronographic control of the drug release. Materials to be used for such purpose includes, but are not limited to; sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose,  
20 hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be  
25 included into the coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the core material.

The coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to,  
30 triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene

glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimised for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

5 In preparation of tablets, either as monolithic drug containing cores for subsequent coating with a delayed release membrane or as a matrix for coated multiple units, additional ingredients may be needed to obtain suitable technical properties such as binders, disintegrants, bulk agents, glidants, lubricants, and coatings agents without effects on the drug release such as water soluble polymers, anti-tacking agents, colourants, pigments and  
10 waxes. Ingredients well known for such usage are for example described in "Handbook pharmaceutical excipients", 2<sup>nd</sup> edition, 1994, Pharmaceutical Press, London.

*Preparation of final dosage form.*

15 Coated units may be filled into hard gelatine capsules or mixed with tablet excipients, such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives, and be compressed into tablets. The compressed tablet is optionally covered with film-forming agents to obtain a smooth surface of the tablet and further enhance the mechanical stability of the tablet during packaging and transport. Such a tablet coat, which may be  
20 applied on a multiple unit tablet or a conventional tablet, may further comprise additives like anti-tacking agents, colourants and pigments or other additives to improve the tablet appearance.

Suitable drugs for the new formulations are IBAT inhibitor compounds such as described  
25 in the above discussed documents, hereby incorporated by references.

The IBAT inhibitor compound could alternatively be a low permeability drug as defined in the Biopharmaceutical Classification System proposed by FDA.

A combination therapy according to the invention should preferably comprise simultaneously, separately or sequentially administration of an IBAT inhibitor compound and a bile acid binder. The IBAT inhibitor could preferably be formulated for ileum delivery and the bile acid binder could preferably be formulation for colon release.

5

#### Use of the invention

The pharmaceutical formulations according to the present invention can be used in the treatment of hypercholesterolaemia. A suitable unit dose will vary with respect to the patients body weight, condition and disease severity. The dose will also depend on if it is to be used for prophylaxis or in the treatment of severe conditions, as well as the route of administration. The daily dose can be administered as a single dose or divided into two or more unit doses. An orally administered daily dose of an IBAT inhibitor is preferably within 0.1 - 1 000mg, more preferable 1 - 100 mg.

15

A pharmaceutical formulation according to the present invention with a targeted delivery in the gastro intestinal tract provides a reduced systemic exposure while maintaining or even increasing the therapeutic effect as can be measured by the area under the drug plasma concentration versus time curve (AUC). The invention provides an enhanced therapeutic effect compared to administration of an IBAT inhibitor in a conventional oral dosage form with drug release in the stomach and/or in the upper part of the small intestine.

A combination therapy comprising an IBAT inhibitor and a bile acid binder comprises preferably a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 2 g. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

25

Claims

1. An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile  
5 acid transport (IBAT inhibitor compound) and a pharmaceutically acceptable carrier  
characterised in that the formulation is designed to deliver the IBAT inhibitor compound  
in the ileum.
2. An oral pharmaceutical formulation according to claim 1 wherein the formulation is  
designed to deliver the IBAT inhibitor compound in the ileum by release in one or more  
10 of the following parts of the body: the distal jejunum, proximal ileum and directly in the  
ileum.
3. The formulation according to claim 1, wherein the carrier is designed to deliver the  
IBAT inhibitor compound in the ileum.
4. The formulation according to claim 1, wherein the carrier is designed to release the  
15 IBAT inhibitor compound in distal jejunum and in the proximal ileum.
5. The formulation according to any of the claims 1 - 4, wherein the carrier is designed to  
give a minimum release of the IBAT inhibitor compound in the upper part of the small  
intestine.
6. The formulation according to any of claims 1 - 4, wherein the pharmaceutical  
20 formulation is a delayed release formulation.
7. The formulation according to claim 6, wherein the formulation provides a lagtime of 0.5  
- 2 hours after emptying the stomach.
8. The formulation according to claim 7, wherein the IBAT inhibitor compound is released  
during the first hour after the lagtime.
- 25 9. The formulation according to claim 6, wherein release of the IBAT inhibitor compound  
from the delayed release formulation is triggered by the pH differences between jejunum  
and ileum.
10. The formulation according to any of claims 1 -9, wherein the IBAT inhibitor compound  
is a low permeability drug as defined in the Biopharmaceutical Classification System  
30 FDA.

11. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with targeted delivery in the gastro-intestinal tract according to any of the claims 1 - 10 to reduce systemic exposure.
12. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with  
5 targeted delivery in the gastro-intestinal tract according to any of the claims 1 - 10 to enhance the therapeutic effect.
13. The use of a pharmaceutical formulation according to any of the claims 1 - 10 in the treatment of hypercholesterolemia.
14. A method for treating hypercholesterolemia comprising treating a subject suffering  
10 from said condition with a pharmaceutical formulation designed according to any of claims 1 - 10.
15. A pharmaceutical formulation for simultaneously, separate or sequential administration in the treatment of hypercholesterolemia which formulation comprises an IBAT inhibitor compound and a bile acid binder.
- 15 16. The pharmaceutical formulation according to claim 15 wherein IBAT inhibitor compound is a low permeability drug as defined in claim 10.
17. The pharmaceutical formulation according to claim 15 wherein the bile acid binder is a resin.
18. The pharmaceutical formulation according to claim 17 wherein the bile acid binder is in  
20 a formulation with colon release.
19. The use of a pharmaceutical formulation according to any of claims 15 - 18 in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.
20. The use of a bile acid binder as prophylaxis or in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.



Abstract.

An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound) and a therapeutically acceptable carrier characterised  
5 in that the formulation is designed to deliver the IBAT inhibitor compound in the ileum.

The IBAT inhibitor compound can also be administered in combination with a bile acid binder to alleviate possible side effects of therapy with IBAT inhibitor compounds, such as for instance diarrhoea. The bile acid binder may be formulated for colon release.

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